REMARKS

I. Status of the claims

Claims 1-34 are pending in this application. Claims 1, 7, 17, 20, 21, 23-29, 31, and 32 were amended in order to more clearly define the subject matter of the invention and not to overcome prior art. No new matter has been added by these amendments. Support for the amendment to claim 1 can be found in the specification at p. 2, paragraph [013]. Support for the amendment to claim 7 can be found in the specification at p. 6, paragraphs [041] to [043]. Support for the amendments to claims 17, 20, 21, 23-26, and 31 can be found in the corresponding original claims. Support for the amendment to claim 27 can be found in the specification at p. 12, paragraph [073]. Support for the amendments to claims 28 and 29 can be found in the specification at p. 10, paragraph [062]. Support for the amendment to claim 32 can be found in the specification at p. 11, paragraph [069].

II. Restriction Requirement

Applicants acknowledge the withdrawal of the Restriction Requirement dated April 23, 2003. All pending claims (claims 1-34) are being examined in this application.

III. Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 17-32 under 35 U.S.C. 112, first paragraph, alleging lack of enablement. The Examiner argues that claims 17-32, drawn to methods of treatment, are directed to the treatment and prophylaxis of various diseases, each of which may have a different cause. The Examiner alleges that "[i]t is inconceivable as to how the claimed compounds can treat the laundry list of diseases embraced by the claims having diverse mechanisms." Office Action dated July 11, 2003 (Office Action),

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at last line of p. 3. The Examiner also argues that there is no disclosure in the specification as to how the *in vitro* data correlates to the treatment of the various disorders of the claims. See p. 3, lines 9-10 of the Office Action. Applicants respectfully traverse these rejections.

The Examiner has not proven a prima facie case of non-enablement

The Examiner has not met his initial burden to show a lack of enabling disclosure in the instant application. The Federal Circuit has clearly indicated that "[o]nly after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility." *In re Brana,* 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995). Except for claim 17, the Examiner did not provide specific evidence of non-enablement against the instant methods of treatment, other than to state, in general terms, that it was inconceivable how the compounds of the invention could treat the various diseases listed in the claims. The Examiner cites Gekle *et al.* (J. Physiol. 520(3):709-721 (1999)) and Cavet *et al.* (Am. J. Physiol. Cell Physiol. 281:C2039-C2048 (2001)) contending that these references indicate low predictability of the activity of NHE inhibitors in the art. However, the passages from these references cited by the Examiner are inapposite to the enablement of the instantly claimed methods of treatment.

For Example, the Examiner cited the following passage in *Gekle*: "More work is required in order to determine the precise role of NHE3 in the regulation of receptor medicated endocytosis and to investigate the mechanisms underlying the establishment of the Na+ gradient across the endosomal membrane." Office Action at p. 4, lines 1-5.

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However, *Gekle* clearly states that NHE inhibitors reduce albumin endocytocis. See point no. 3 in Summary section, p. 709; see also, e.g., the Results section and Figure 5. *Gekle* does not dispute that NHE3 reduce albumin endocytosis. Rather, *Gekle* is interested in determining the particular role NHE3 plays in albumin endocytosis (the mechanism of action of NHE3). The Examiner is respectfully reminded that it is not necessary for patentability purposes to know the exact mechanism by which a process occurs. See *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 U.S.P.Q. 1137, 1140 (Fed. Cir. 1983). It is only necessary to show that the process works. Here, *Gekle* clearly demonstrates that NHE3 inhibitors reduce albumin endocytosis. Therefore, the passage cited by the Examiner regarding the lack of knowledge about how that process is exactly carried out is not relevant to the enablement of the instant methods of treatment.

Similarly, the passage cited by the Examiner from *Cavet* does not speak to the issue of enablement of the instant methods of treatment. The passage cited states that '[a]lthough [NHE2 and NHE3] are located on the apical surface of renal and intestinal epithelial cells, in many species their relative roles have not yet been fully defined." Office Action at p. 4, lines 5-7. However, *Cavet* also identifies a general function for NHE: "[t]he Na^+/H^+ exchangers (NHEs) are a family of membrane transport proteins that catalyze the electroneutral exchange of intracellular H^+ for extracellular Na^+." *Cavet* at p. C2039, col 1. In any event, the Examiner has failed to indicate how the statement in *Cavet* prevents enablement of the instant invention, especially because *Cavet* is silent with respect to the effect of inhibitors of NHE3 in the treatment of any of the diseases cited in the instant claims. As explained before, it is not necessary for patentability

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purposes to know the exact mechanism by which a process occurs. Applicants cite various references that support the enablement of the methods of the invention in the next section.

Therefore, having provided no specific evidence that the instantly-claimed methods are inoperative, the Examiner has not met his burden of proving lack of enablement for the instant claims. For at least this reason, Applicants respectfully request that this rejection be withdrawn for claims 18-32.

The Examiner asserts that claim 17 "is drawn to the 'treatment of a cell proliferative disorder.'" However, claim 17 is drawn to a "method for the treatment of a disorder of the respiratory drive." Although instant claim 30 is drawn to a "method for the treatment of a disease in which cell proliferation is a primary or secondary cause," Applicants have not been able to find the specific text cited above by the Examiner in the instant claims. Applicants address this rejection and present further arguments in support of the enablement of claims 17-32 in the next section.

The specification and the level of one of ordinary skill in the art enable the claimed methods of treatment

A common characteristic of the various diseases cited in the instant claims is the fact that all of them may be caused by an abnormal function of NHE, or can be alleviated by the administration of NHE inhibitors. One embodiment of Applicant's invention is drawn to a new class of NHE3 inhibitors. Specification at p. 9, paragraph [059]. Several methods of treatment using NHE inhibitors are known in the art (see below). The Examiner is reminded that enablement is analyzed, *inter alia*, in light of the level of one of ordinary skill in the art. M.P.E.P. § 2164.01(a). The following

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references assist in confirming that NHE inhibitors can be used in the treatment of the diseases mentioned in claims 17-32. The references, therefore, corroborate the teachings in the specification that fully enable the skilled in the art to use the claimed methods of treatment. Copies of the following references are enclosed for the Examiner's convenience.

Reference for claims 17-20

Kiwull-Schone et al. (American J. Respiratory and Critical Care Medicine, 164(7):1303-11 (2001), published by some of the inventors of the present invention, shows that NHE3 inhibitors augment the phrenic nerve activity and reduce the pCO_2 necessary to maintain breathing (pCO_2 apneic threshold). See, e.g., Abstract. Such reduction demonstrates that NHE3 inhibitors aid in the treatment of a disorder of the respiratory drive.

Additional reference for claims 18-19

Abu-Shaweesh et al. (Pedriatic Research 525(3):459-464 (2002)), also published by some of the inventors of the present invention, shows that NHE3 inhibitors reduce the duration of apneas and "possibly reduce the pathophysiological consequences of potentially life threatening apnea in infants." See, e.g., the title and Abstract.

Additional reference for claim 20

Low pharyngeal tone during sleep (muscular relaxation) leads to both snoring and obstructive apneas. Snoring is always associated with obstructive apneas (See, e.g., Horner, R-l., Respir. Physiol, 119(2-3):113-21 (2000)). Moderate lowering of pharyngeal muscle tone leads to snoring while severe lowering of pharyngeal muscle or additional disturbances lead to obstructive apnea (plus heavy snoring). NHE3 inhibitors

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would be effective in the treatment of snoring by increasing motor neuron output to upper and lower airways as shown in *Kiwull-Schone* (reference for claims 17-20 above). Increasing the muscle tone of the upper airways suppresses snoring. See specification at p. 11, paragraph [065].

References for claims 21-22, and 26

Hropot et al. (Kidney International, 60(6):2283-2289 (2001)) clearly indicates that NHE3 inhibitors attenuate ischemia-induced acute renal failure. See, e.g., Abstract. This reference also corroborates the treatment of a condition of a peripheral organ (in this case the kidney) by the action of NHE3 inhibitors (claim 26). Drumm et al. (European J. of Medical Research, 6(10):422-432(2001)) shows that NHE3 inhibitors reduce albumin-induced renal interstitial inflammation and fibrosis (a type of chronic renal failure).

Reference for claim 23

Schultheis et al. (Nature Genetics, 19(3):282-85 (1998)) shows that mice lacking NHE3 function present slight diarrhea. See, e.g., Abstract. Furthermore, *Schultheis*' data "show that NHE3 is the major absorptive Na^+/H^+ exchanger in kidney and intestine, and that lack of the exchanger [e.g., by inhibition of NHE3] impairs acid-base balance and Na^+-fluid volume homeostasis." *Schultheis* at Abstract.

References for claim 24

Silviani et al. (J. Hepatology 26(6):1281-1286 (1997)) and Colombani et al. (Clinical Science 91(2):209-12 (1996)) show that NHE3 is present in human gallbladder. These references suggest that NHE3 plays a role in water and electrolyte absorption from bile. See e.g., the abstracts of *Silviani* and *Colombani*. These findings indicate

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that NHE3 inhibition could be beneficial in the prevention of gallstone formation. See also the specification at p. 11, paragraph [068].

References for claim 25

Horikawa et al., (Pharmacology 63(2):76-81(2001)) and Kuribayashi et al. (International Journal of Tissue Reactions, 21(2):29-33 (1999)) show that NHE inhibtors reduce cerebral infarction (an ischemic condition of the central nervous system), which indicates that the compounds of the invention can also be used to treat a stroke.

Reference for claim 27

Claim 27 has been amended to better define the invention by reciting treatment of an ischemia-induced endogenous state of shock. This type of shock leads to a deficiency in blood volume. Due to this decrease, the blood level may not be sufficient to maintain blood circulation. This collapse in circulation causes a deficiency of oxygen in the tissues deprived of blood and results in ischemic damage, such as kidney failure. Therefore, treatment of this type of shock is corroborated by the references that support the treatment of an ischemic condition. See, e.g., the references cited in support of claim 25.

References for claims 28-29

Kim et al. (Annals of Thoracic Surgery 66(2):436-42(1998)) and Kim et al. (Cardiovascular Surgery 6(1):67-75 (1998)) clearly demonstrate that NHE inhibitors preserved hearts during transplantation and storage. See, e.g., the Abstract of both references.

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References for claim 30

Kapus et al. (J. Biol. Chem. 269(38), 23544-52 (1994)) indicates that "[w]hile antiporter-deficient cells [cells that did not express NHE1, NHE2, and NHE3] were unable to grow at acidic pH levels, all three isoforms supported proliferation under these conditions." *Kapus* at abstract. This statement shows that cell proliferation is prevented in cells lacking functional activity of NHEs (such as, for example, through inhibition of the NHEs). Additionally, the results in Wang et al. (J. Biol. Chem. 272(42), 26545-49 (1997) "show that the absence of Na+/H+ antiport [e.g. through inhibition of the NHE] as a pH regulatory mechanism can result in deficiencies in both cell growth and differentiation embryonal carcinoma cells." Therefore, both *Kapus* and *Wang* support the inhibition of cell proliferation by inhibition of NHE.

Reference for claim 31

The use of NHE inhibitors for normalizing serum lipids has been described in PCT patent application WO97 46,226.

Reference for claim 32

Petzel et al. (Experimental Biology 2000, Congress Abstract April 15 to 18, 2000) shows that NHE3 inhibitors decrease fluid secretion in the blood-feeding MT mosquito, which is considered an ectoparasite. Because fluid secretion is vital to the mosquito's survival, treatment with NHE3 inhibitors could be an effective means to treat an infestation by said mosquito.

In light of the foregoing references and remarks, Applicants respectfully request that the rejection of claims 17-32 be withdrawn.

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The Examiner further argued that the specification does not enable prophylaxis of the diseases cited in the claims. Applicants traverse this rejection. However, with the purpose of expediting prosecution, Applicants have amended the relevant claims by deleting references to prophylaxis. Applicants reserve the right to pursue the subject matter currently deleted from the claims at a later stage in the prosecution of this application or in continuation or divisional applications.

IV. Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-32 under 32 U.S.C. 112, second paragraph for allegedly being indefinite. The Examiner argues that the term "heterocyclo-norbornylamino derivative" in the preamble of claim 1 is improper Markush language. Applicants disagree that the claim is indefinite, but in the interest of expediting prosecution, Applicants amended claim 1 following the suggestion the Examiner made in the Office Action. This amendment does not change the scope of the claim. Applicants respectfully request that this rejection be withdrawn.

The Examiner argues that claim 7 lacks the definitions of variables A' and A". Applicants have amended claim 7 by defining A' and A" as disclosed in the specification on page 6, paragraph [043]. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Examiner argues that it is not clear what is intended to claim in claims 28, 29, and 32. Applicants have dealt with these rejections by amendment. Accordingly, Applicants respectfully request that these rejections be withdrawn.

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Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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By: _____
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Dated: November 12, 2003

Enclosures: Copies of the references cited in this Response and Amendment

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